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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

KOEBERL et al

Atty. Ref.: 01579-1155; Confirmation No. 3856

Appl. No. 10/761,530

TC/A.U. 1652

Filed: January 21, 2004

Examiner: Raghu, G.

For: CONSTRUCTS FOR EXPRESSING LYSOSOMAL POLYPEPTIDES

\* \* \* \* \*

August 7, 2008

Mail Stop AF  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

AMENDMENT UNDER RULE 116

This is in response to the Office Action dated December 5, 2007, in the above matter, a Notice of Appeal having been filed April 7, 2008 and the period for filing an Appeal Brief having been extended up to August 7, 2008, by submission of the required petition and fee herewith. The following comments are offered.

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REMARKS/ARGUMENTS

Reconsideration of this application is respectfully requested.

Claims 1, 2, 5, 8-12, 14-16, 18, 21, 22 and 24-29 stand rejected under 35 USC 102(b) as allegedly being anticipated by Amalfitano et al. The rejection is again traversed.

Claim 1 (from which the other claims subject to this rejection depend) relates to a nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human GAA. Claim 1 requires that the secretory signal sequence replace the leader sequence of native human GAA. It is again submitted that Amalfitano et al includes no such teaching.

In rejecting the claims as anticipated, the Examiner makes reference to the paragraph beginning at line 13 on page 22 of Amalfitano et al. The referenced portion of the citation indicates that an adenovirus vector can be used to infect a cell in culture to produce a polypeptide of interest, lysosomal acid  $\alpha$ -glucosidase is given as an example (at page 28, to which the Examiner also refers, reference is made to human GAA). The referenced portion goes on to indicate that “[s]ignal peptide sequences that direct extracellular secretion of proteins are known in the art and nucleotide sequences encoding the same can be operably linked to the nucleotide sequence encoding the polypeptide of interest by routine techniques known in the art”. The Examiner also refers to Figures 4A-B and 5A-C and the related descriptions of those figures and experimental details. These figures relate to studies involving the LacZ gene.

While the Examiner cites pages 3-41 of Amalfitano et al generally and, especially, pages 6, 7, 12, 22, 26, 28-30, 35 and 41, and Examples 1, 4, 9 and 13, the Examiner fails to indicate where Amalfitano et al teaches replacing of the leader sequence of native human GAA with a secretory signal sequence, as required by claim 1. The Examiner is urged to properly support the rejection or withdraw same.

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Claims 1, 2, 5, 8-12, 14-16, 18, 21, 22 and 24-29 stand rejected under 35 USC 102(b) as allegedly being anticipated by Van Bree et al. The rejection is traversed.

Van Bree et al teaches at page 8, lines 18 and 19 "operably linking a DNA sequence encoding the [lysosomal] protein with a signal sequence, a promoter and an enhancer". A portion of Van Bree et al to which the Examiner specifically refers (page 9, lines 16-30) indicates that the signal sequence "must be capable of directing the secretion of the lysosomal protein to the mammary gland" and that suitable sequences "can be derived from mammalian genes encoding a secreted protein".

The Examiner makes general reference to pages 3-28 of Van Bree et al and "especially pages 7, 9 and 10." However, no where is Van Bree et al seen to teach the replacement of the leader sequence of native human GAA with a secretory signal sequence, as required by the instant claims. The Examiner is urged to point out where such a teaching is found or withdraw the rejection.

Claims 3, 4, 73, 75, 77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and Haseltine et al. The rejection is traversed

The present invention results, at least in part, from studies designed to test the hypothesis that chimeric lysosomal polypeptides containing an alternative signal peptide could increase the secretion of lysosomal polypeptides from transduced cells and enhance receptor-mediated uptake of lysosomal polypeptides in tissues. As evidenced by the data presented in the application (and in Sun et al, Mol. Ther. 14:822 (2006) – of record), replacement of the lysosomal leader sequence (which targets the polypeptide to the lysosome) by a secretory signal peptide, increased secretion from cultured cells (see, for example, Fig. 15 of the application). Further, receptor mediated uptake of the chimeric polypeptide occurred efficiently (see, for example, Table 1 of

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Sun et al, Mol. Ther. 14:822 (2006)). The uptake was inhibited by mannose-6-phosphate thereby implicating the involvement of mannose-6-phosphate receptors.

As detailed above, Amalfitano et al does not teach replacement of the leader sequence of native human GAA with a secretory signal sequence. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Haseltine et al's teaching of the albumin signal sequence provide such a teaching. Further, it is only with hindsight that the references relied upon would have been combined as the documents themselves do not suggest their combination. Accordingly, the rejection is clearly not well founded and withdrawal of same is requested.

Claims 1-3, 5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Martin et al. The rejection is traversed.

The deficiencies of Amalfitano et al are discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Martin et al's teaching of an erythropoietin signal peptide the albumin signal sequence would have brought one skilled in the art closer to the claimed invention. Further, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Accordingly, reconsideration is requested.

Claims 1-3, 5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Whitfeld et al. The rejection is again traversed.

The fundamental deficiency of Amalfitano et al is discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Whitfeld et al's teaching of an  $\alpha$ -1-antitrypsin secretory signal sequences would have cured the failing of the

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primary reference. Further, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

Claims 1-3, 5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Meulien. The rejection is traversed.

The deficiency of Amalfitano et al is described above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Meulien's teaching of a Factor IX secretory signal sequence would have cured the failings of Amalfitano et al. Further, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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